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The Structural and Functional Connectome and Prediction of Risk for Cognitive Impairment in Older Adults

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Abstract

The human connectome refers to a comprehensive description of the brain's structural and functional connections in terms of brain networks. As the field of brain connectomics has developed, data acquisition, subsequent processing and modeling, and ultimately the representation of the connectome have become better defined and integrated with network science approaches. In this way, the human connectome has provided a way to elucidate key features of not only the healthy brain but also diseased brains. The field has quickly evolved, offering insights into network disruptions that are characteristic for specific neurodegenerative disorders. In this paper, we provide a brief review of the field of brain connectomics, as well as a more in-depth survey of recent studies that have provided new insights into brain network pathologies, including those found in Alzheimer's disease (AD), patients with mild cognitive impairment (MCI), and finally in people classified as being "at risk". Until the emergence of brain connectomics, most previous studies had assessed neurodegenerative diseases mainly by focusing on specific and dispersed locales in the brain. Connectomics-based approaches allow us to model the brain as a network, which allows for inferences about how dynamic changes in brain function would be affected in relation to structural changes. In fact, looking at diseases using network theory gives rise to new hypotheses on mechanisms of pathophysiology and clinical symptoms. Finally, we discuss the future of this field and how understanding both the functional and structural

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Compliance with Ethics Standards

Human and Animal Rights and Informed Consent Deidentified human MRI data was included in Figure 1. Source scans were collected under an IRB-approved protocol at the Indiana University School of Medicine. No other data from human subjects was collected for this review article.

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connectome can aid in gaining sharper insight into changes in biological brain networks associated with cognitive impairment and dementia.

Keywords

Brain connectomics; Neurodegenerative disease; Network science; Cognitive impairment

Introduction

The average life expectancy has steadily increased with respect to each previous generation. As the mean age rises, experimental evidence indicates a greater decline of sensory, motor, and cognitive functions in the elderly population [1]. Given that abnormal aging can result from a variety of factors (such as genes or environment or lifestyle), cognitive impairment associated with aging is considered a systemic problem. Therefore, effective prediction of successful aging versus cognitive decline becomes difficult. Aiming to face this complexity, interest in early markers of cognitive impairment has grown, since it is widely regarded as an early marker of dementia. Recently, hope has been placed in identifying biomarkers that predict risk for developing cognitive impairment. Given advances in non-invasive neuroimaging techniques and in network analysis, the emerging field of brain connectomics is increasingly well situated to link cognitive impairment with structural and/or functional network changes. These changes may be reflected in a number of topological features that cover global and local aspects of the brain organization and communicability.

For the reader's convenience, a glossary is presented for terms related to network science. Throughout this review words in *italics* will refer to items present in Table 1 which includes a glossary of network indices.

The Human Connectome

The concept of the human brain as a large-scale complex *network* termed “connectome” was originally introduced in 2005 [2]. The key proposal was to model the brain as a *network*, with the different gray matter regions acting as *nodes*, and their *structural connectivity* (*SC*) through white matter fiber bundles as *edges*. As the first drafts of the human connectome became available [3] an increasing interest in applying graph theory to human neuroimaging data (specifically to diffusion weighted imaging (DWI)) emerged. This helped to uncover topological features of the *structural connectome* such as *small world-ness*, highly connected *hubs*, and *modularity*. It also allowed modeling and visualization of the most prominent white fiber tracts constructed from bundles of *streamlines* connecting different brain regions, an important first step in identifying the basic layout of the brain's *SC* and its relation to *functional connectivity* (*FC*) [4]. Interestingly, the basic idea of the brain as a structural *network* of connected neurons with functional implications was proposed years, if not decades, before the idea of the connectome. The foundational writings of Santiago Ramon y Cajal were a first antecedent of the neuronal *networks* we now know [5]. His work and intricate circuit diagrams unveiled individual neurons and their synapses. In comparison, the field of brain connectomics works at a much coarser grain scale and aims to model and assess the complex interactions between neural populations (as divided by regions) to

understand the behavior of the system overall. In turn, brain connectomics uses network science to handle the complex methodologies needed to understand the dynamic interactions of different brain regions both functionally and structurally and how these interactions might influence cognition.

The Structural and Functional Connectomes

Using DWI to assess *SC* by modeling white matter fiber tracts, *SC* information can be represented as a binary *network* where *nodes* represent brain regions and *edges* represent the presence or absence of fibers connecting those regions. To further elaborate this *network* representation, it is possible to gather fiber descriptors such as number of *streamlines*, fiber integrity as measured by *fractional anisotropy (FA)*, the spatial trajectory of fibers, the estimated length of these fibers (in millimeters, *fiber length*), and composites such as fiber density [3, 6] between pairs of brain regions. This collection of fiber descriptors allows weighted representations of *SC* (see Fig. 1a, b), which more fully defines the physiological effects and capacity for plasticity changes within the structural connectome. In contrast to structural connections, functional connections refer to statistical dependencies among time series of neuronal activity or blood oxygen level dependent (BOLD) signals, often expressed simply as linear Pearson correlations. Functional connections are time-dependent and can fluctuate on time scales as fast as seconds (fMRI) or even hundreds of milliseconds (EEG, MEG). Recent work has shown that functional connections exhibit dynamic changes during rest as well as reconfiguration in the context of different stimuli and tasks [7].

Systematic assessment of resting-state *FC* has led to the concept of the “*functional connectome*.” In a landmark study employing resting-state functional MRI (RS-fMRI), Biswal and colleagues found that looking at BOLD signal fluctuations that occur at a lower frequency (<0.1 Hz) revealed patterns of coherent spontaneous fluctuations among spatially remote and distinct brain regions [8]. This seminal work spurred further studies to confirm the existence of synchronous spontaneous fluctuations between different areas in the brain, revealing coherent components that were highly consistent among individuals [8–12]. Low frequency, spontaneous (BOLD) fluctuations that occur at rest are referred to as intrinsic brain activity and its correlated components represent so-called resting-state networks (RSNs) [11, 13]. Note that RSNs refer to components or sub-networks within the cortex; hence, the broad term “*network*” denotes here a set of regions or even voxels showing high functional coherence within the sub-network and low functional coherence with the rest of the system. There has recently been significant work demonstrating the validity and biological underpinnings of using temporal correlations found in RSNs to infer *FC* [14–18]. By studying the relationships between spontaneous BOLD signals in different/distinct brain regions, multiple RSNs have been identified (see Fig. 1d–f). RSN analysis allows for a functional based assessment of *network* differences between subjects or clinical groups, while greatly reducing the dimensionality of the approach, from thousands of voxels to a few prominent sub-networks. For instance, differential connectivity between subjects with impaired cognition and normal cognition in the default mode network (DMN, one of the earlier [19] and most well-studied *networks*) suggests that *FC* is sensitive to pathology and its assessment may improve diagnostic methods.

The Human Connectome and Normal Aging

Research on structural and functional brain *networks* has jointly given rise to the field of brain connectomics. Network science and graph theory have furthered this advancement by providing a suitable framework to quantify and give objective meaning to *SC/FC* or brain connectomics changes. For instance, using these tools, Betzel and colleagues examined how the connectome changes with aging and found that indeed both *SC* and *FC* evolve or “re-organize” during aging [20]. According to the study, several RSNs *FC* decreased with healthy aging, while other RSNs experienced an increase in *FC*. Changes were also observed in *SC*, including an overall decrease in the density of anatomical connections between brain regions and an overall loss of white matter fiber tracts as age progressed. This paper added evidence that *FC* and *SC* are closely related and encourage further exploration of how age-related changes in *SC* and *FC* correlate with changes in behavior and cognition.

Further research on the aging connectome found that the topology of important “*hubs*” or highly connected regions in the structural connectome of older adults tended to remain similar to the young adult population, with only subtle gender differences in terms of *fiber length* [21]. The preserved *hub* regions included subcortical structures such as the thalamus, striatum, and the amygdala, as well as cortical regions such as the anterior cingulate, insula, and precentral gyrus, which were consistent with other adult structural *network* studies [22, 23]. This indicates that there is some topological *network* stability across normal aging, which has strong implications for healthy large-scale *network* communication and might support the preservation of memory and executive functions in normal aging.

Using Connectomics to Study Alzheimer’s Disease

As dementia continues to become more prevalent, the field of brain connectomics is quickly evolving to not only study human connectome disruptions that occur as a function of normal aging but disruptions in neurodegenerative disorders as well [24, 25]. Many brain connectome studies have already begun generating exciting results regarding the dysfunction occurring in neurodegenerative disorders. Relative to studies focalized in a particular region of interest or in a relatively small targeted neural circuit, brain connectomics provides amore systemic view by modeling whole brain *networks*. In this way, brain connectomics can assess whole brain organizational changes or disruptions. AD is often thought of as a disconnection disorder in that a lesion or plaque in one region of the brain can disrupt healthy communication between other brain regions resulting in an eventual overall reduction of connections required for healthy cognitive functioning [26]. As a result, changes in brain *networks* have begun to be looked at extensively in AD [27–33]. Analyses of *SC* and *FC* in AD have given rise to new hypotheses of the underlying pathophysiology of AD. Further, they can also be used to understand new correlations with clinical and cognitive symptoms that cannot be explained from a single region or connection [33]. Table 2 summarizes a list of recent studies focused on using *SC* and/or *FC* in those at risk for and with AD.

The Connectome in AD and MCI

Analyzing the structural connectome of AD patients has shown disruptions in connectivity in the cingulum bundle tract, the corpus callosum, and the superior longitudinal fasciculus ([34–37]; for additional information, see [38]). Patients with mild cognitive impairment (MCI), which is considered a prodromal stage of AD, have also been shown to exhibit many of these same disruptions, although not as severely as seen in AD. This further supports MCI as an intermediate state between healthy aging and AD ([39–41]; additionally, see review [42]). Another study also found significant abnormalities in a crossing fiber region known as the centrum semiovale (close to an important *hub* region, [6]) only in MCI patients compared to cognitively healthy age-matched controls [39]. When looking at whole brain diffusion differences, MCI patients were found to have a higher mode of *FA* values in this region than cognitively healthy age-matched controls. Mode of *FA*, in this case, refers to the shape of diffusion ranging from -1 (indicating less directionality) to $+1$ (indicating more directionality). The study also revealed that their patient population (AD) had higher *FA* values in these regions. Together, this evidence suggests a selective degeneration in crossing fiber pathways. This result is important for two reasons: (a) it demonstrates that diffusion MRI is able to detect subtle changes in the structural connectome between disease states and (2) it highlights the need for further interpretation of both increases and decreases in *SC* with regards to the underlying neuropathology. Overall, changes in the fiber tracts provide evidence of a disruption of whole brain organization in prodromal and clinical AD through damage to *hub* regions.

Important findings have also been reported regarding *FC* in AD. Many studies have already found significant *FC* changes in AD patients [43, 44]. For instance, patients with severe AD showed reduced amplitude of fMRI oscillations, as well as reduced *FC* strength, specifically in long-distance *FC* connections, when compared to mild and moderate AD patients [45]. A reduction in *clustering* and *modularity* was also observed in patients with AD compared to cognitively healthy age-matched controls, indicating a less segregated or modular nature of connectivity, and hence a more disorganized way in which brain regions communicate [46–48]. Finally, studies using graph theory to assess *SC* have also allowed us to better understand the relationship of *SC* and *FC* as AD progresses [31].

Other metrics have also been used to measure the way different pathways break down in AD. One such metric is the *k-core*, which is a measure that assesses the overall connectedness of a *network* by identifying the most highly interconnected sub-networks within a global *network* [6]. As opposed to looking at a whole connectivity matrix that may include unreliable connections making it difficult to pull out meaningful disease effects, using the *k-core* can enhance detection of changes that may be caused by the disease. This is accomplished by looking at deeper highly connected sub-networks or *cores*. In AD patients, *k-core* analysis revealed that there was a complete loss of all *core networks* in the left hemisphere indicating a dramatic unilateral change in brain *network* topology as disease progresses [49, 50]. This finding suggests that there is a loss of healthy organizational structure in the brains of AD patients. Similarly, Daianu and colleagues assessed structural *cores* of the brain in AD patients and found that structural brain connectivity was affected according to a variety of *network* metrics that describe the topological organization of the

brain [51]. Disrupted functional whole brain connectivity in cortical *hubs* was also reported in patients with MCI [48]. Evaluation of other *SC* measures revealed a similar story; *nodal degree* decreased as the disease progressed, as did *path length* and *efficiency* [50, 51]. It has recently been shown that not all structural *core networks* are disrupted in AD. Specifically, AD more strongly affected low-degree brain regions rather than the high-degree *nodes* that form a *rich club*, leaving this low-degree *network* better preserved [52]. However, more research is needed to better understand the *SC* and *FC* changes in AD and their impact on clinical and cognitive decline.

The Connectome in Populations at Risk for AD

AD is believed to have a prolonged prodromal and preclinical phase initially characterized by the development of silent pathologic changes, including the development of amyloid-beta (A β) plaques and neurofibrillary tangles caused by hyperphosphorylated tau, with no clinical symptoms [53–56]. Thus, cognitively normal individuals with significant amyloid and tau pathology (assessed either by measuring cerebrospinal fluid (CSF) levels or by positron emission tomography (PET) techniques) are at high risk for progression to AD [57–60]. Other changes in brain *network* structure and function may also be present in the preclinical phase of AD. For instance, one group set out to measure *FC* in the DMN using *independent component analysis* (ICA) in a distinct preclinical group (marked by individuals who have cognitive complaints yet have normal psychometric performances) along with an MCI group and healthy controls. It was found that the preclinical group, identified as informant-verified cognitive complainers (CC), demonstrated lower connectivity in the DMN, a RSN known to be disrupted in AD, compared to cognitively healthy age-matched controls without complaints yet have higher connectivity compared to the MCI group [61]. In another study by the same group, diffusion tensor imaging revealed white matter changes between diagnostic groups as measured by *FA* values in regions associated with AD. Their main findings revealed lower *FA* values in parahippocampal WM among the MCI group compared to cognitively healthy age-matched controls, as well as intermediate *FA* values in the CC group falling between MCI and cognitively healthy age-matched controls without complaints. These studies added evidence to the existence of a preclinical intermediate state using connectivity measures [62]. Another group, Drzezga and colleagues, used CSF measures to show that asymptomatic individuals with increased amyloid burden demonstrated subtle whole brain *FC* disruptions and hypometabolism (as measured through [18 F]fluorodeoxyglucose PET) [48]. While the pathology of this preclinical category is still unclear, these studies indicate that connectomics can capture early functional and structural changes. This may be a consequence of emerging molecular AD pathology.

Genetic markers have also helped identify asymptomatic people with high risk for AD. The major genetic risk factor for late-onset AD is the $\epsilon 4$ allele of the apolipoprotein E (*APOE*) gene on chromosome 19 [63]. An early study demonstrated that asymptomatic *APOE* $\epsilon 4$ carriers exhibited an increase in the magnitude and extent of brain activation during a verbal memory task in brain regions known to degenerate in AD. Furthermore, these same subjects were re-tested 2 years later and brain activation in the previously identified areas correlated with the degree of memory decline [64]. More recently, cognitively intact carriers of the *APOE* $\epsilon 4$ allele have been linked to accelerated age-related decline in local interconnectivity

of structural brain *networks* [65], as well as disruption in the functional connectome [66], relative to *APOE* $\epsilon 4$ non-carriers. Cognitively normal *APOE* $\epsilon 4$ carriers also show differences in large-scale brain functional *networks* (i.e., decrease in nodal *efficiency* in medial temporal areas) and structural connections (aberrant regional topological patterns in temporal lobe and other regions) [67]. Interestingly, Wang and colleagues found reduced *efficiency* in whole brain topological organization, as well as decreased intramodular connectivity, within the posterior DMN and executive control *network* in *APOE* $\epsilon 4$ carriers with AD relative to non-carriers [66]. Impaired functional *hubs* and their *rich club* connections with other RSNs were also found in *APOE* $\epsilon 4$ AD patients indicating differential brain *network* organization as a function of *APOE* $\epsilon 4$ variants in AD. These studies explore the connectome by combining different imaging modalities and a network science approach suggest that these tools can help elucidate changes that would otherwise be undetectable in a high-risk, preclinical population.

Recent Developments

While the continued development and refinement of RS-fMRI [68–70] and DWI methods [71] hold great promise for understanding biological changes associated with normal aging and dementia so can integrating genomic data. The combination of improved neuroimaging methods to measure biological processes and genetic information from across the genome is likely to provide a more complete picture of health and disease. Genetic analysis may also be incorporated with DWI data. Indeed, the diffusion properties of white matter, placement of fiber tracts, and overall *SC networks* are thought to have strong heritability [72]. White matter integrity (as measured by *FA*) was found to show a strong genetic influence, specifically in the bilateral frontal and parietal lobes and the left occipital lobe. Results from a larger family-based study from Kochunov and colleagues supported high heritability of white matter diffusion properties, showing that average measures for *FA* and *radial diffusivity* were highly linked to genetics [73]. Overall, these studies suggest that the microstructure of cerebral white matter is at least partially genetically determined. Imaging genetics with DWI data has also been applied to dementia research. Jahanshad et al. evaluated the influence of gene variants or “polymorphisms” on *SC* and found that variations in a gene known as *SPON1* affected *SC* in an older adult population with varying degrees of cognitive impairment [74]. Furthermore, older adults who carried the variant associated with increased *SC* had less severe dementia scores and a lower risk of AD. This discovery of *SPON1* variants associated with brain connectivity suggests a new neurogenetic pathway with links to dementia severity that can be further explored.

Genomic data may also help elucidate the biological basis for the synchronous low frequency fluctuations that are suggested to give rise to brain *networks* using RS-fMRI. One study found that expression of 136 genes (later identified to be involved in ion channel formation) were significantly associated with RS-fMRI measures in humans and significantly associated with axonal connectivity in a rodent model [75]. Additionally, Richiardi and colleagues demonstrated that functional brain *networks* as defined by RS-fMRI are significantly correlated with gene expression data. Their data revealed that functional *networks* are associated with a set of genes that code for ion channels and other important synaptic functions (i.e., dopamine neurotransmitter release), further supporting a

strong biological foundation of RSNs. The results from these studies provide additional evidence that integrating gene expression and brain connectivity measures can provide insight into the molecular mechanisms underlying not only functional *networks* but also structural networks. Other studies have found that an altered expression of genes associated with AD can translate to altered *FC* at the molecular level [76]. These studies integrating RS-fMRI and genomics suggest that the connectome may offer a rich and promising target for genetic analysis.

Another future direction of brain connectomics is through the integration of different technologies, specifically studies that integrate multiple imaging modalities [77]. Multimodal imaging refers to the integration of data from more than one imaging modality, such as DWI, RS-fMRI, EEG, and PET. This integration typically occurs at the level of statistical analysis where each modality has an influence over the end result. Additionally, the data can be integrated in a more exploratory fashion, where the comparison is more qualitative than quantitative. For example, data analysis has been treated in this way with disorders such as autism spectrum disorder (ASD). ASD has been conceptualized as a breakdown of neural communication and connectivity. Integration of multimodal imaging techniques has shown significant promise in elucidating brain connectomics in ASD. Over the last decade, theoretical accounts of ASD have shifted towards emphasizing the breakdown of neural communication and connectivity much like AD. In light of this shift, the use of multimodal imaging has begun to show promise. Studies in ASD show convergence of altered *SC* and *FC* within the same regions, including regions of the medial prefrontal cortex and posterior cingulate/precuneus that are core members of specific RSNs [78–80]. Additionally, a convergence in altered function, volume, and connectivity of frontal regions involved in executive function, language, motor, and sensorimotor functions was also found in ASD [81–83]. Finally, a study revealed age-related differences in the coupling of function and structure in healthy controls that did not occur in ASD patients.

Multimodal neuroimaging are also useful for achieving the best possible spatial and temporal resolution (i.e., EEG and fMRI [84]) as well as for using data from one modality to constrain the interpretation of another modality. In the latter case, the purpose of multimodal imaging would not be to merge data but to assist with informed judgment of the data within a broader context. For instance, EEG data measuring participant alertness has been used to inform interpretation of fMRI data [84]. Ultimately, multimodal imaging has the potential to help obtain a more comprehensive physiological view of brain processes both in healthy adults and patients.

As a complement to the challenges and opportunities of this technological integration, the area of brain connectomics is also evolving from a theoretical point of view. Multimodal imaging naturally allows us to elaborate on multiplex or multi-layered *networks* [85, 86], where one system is not represented by a unique adjacency or connectivity matrix, but by more than one, attending to different features or to the different nature of their connections. Another emergent area of research consists of *network* morphospaces [87–90] where *networks* occupy a space in n-dimensional systems that obey to different trade-offs of *network* characteristics. This incorporation of information from theoretical concepts [91]

into brain connectomics is expanding the way we understand communication within *networks* [92, 93] and in the human brain [94, 95].

Finally, another innovation in modeling *FC* is the emergence of dynamic RS-fMRI. Until recently, most RS-fMRI studies looked at data in a stationary framework to interpret results. While studies employing this framework have uncovered large-scale properties of brain function, the resulting characterization ultimately represents an average across complex spatiotemporal phenomena. Quantifying changes in *FC* metrics over a longer scan (10 min or longer) may provide greater insight into fundamental properties of brain *networks* and how they change over time [96]. Recent studies have demonstrated that correlations among brain regions, both within and between *networks*, indeed evolve over time [7, 97–99]. These results suggest that resting brain activity can be divided into subsets or “communities” of brain regions that strongly interact for a time but that these interactions are not static. For instance, low frequency BOLD signal fluctuations revealed synchronized communities reoccurred intermittently in time and across scanning sessions during RS-fMRI scans [100, 101]. In addition, the synchronized communities constitute components of previously defined RSNs known to be engaged in sensory-motor or cognitive function. As discussed earlier, altered static *FC* in RSNs has been found in AD patients. Thus, it would be of great interest to see if using a non-static or “sliding-window” approach would provide an even more accurate description of *FC* changes in AD. One of the first reports demonstrating RS-fMRI changes in AD patients beyond the traditional average *FC* metrics [102] reported impairments in the dynamics of spontaneous activity by examining time varying changes of a *modularity* metric [103]. Using dynamic *FC* representations, the authors reported differences in the “dwell time” within different sub-network configurations of the DMN between AD and cognitively healthy age-matched controls. In other words, less time was spent in brain states with strong posterior DMN region contributions and more time in states characterized by anterior DMN region contributions in AD patients. This observation has the potential to lead to a better understanding of the large-scale characterizations of AD and potentially a more accurate prognostic picture. This early work offers great promise in revealing aspects of dynamic *FC* at a macroscopic scale.

Conclusion

The increased sensitivity and whole brain perspective of *SC* and *FC* measures assessed using diffusion weighted MRI and RS-fMRI, respectively, have already provided numerous insights into the specific disturbances of *network* organization that occur in the diseased brain. For instance, normal cognitive aging results in changes in brain network features but are mainly localized in hub regions in the frontal, parietal, and occipital lobes. However, it is important to note that, overall, brain networks have been shown to have high topological *global efficiency* despite aging. While significant topological modification is observed with brain maturation, the general structure of the connectome remains stable over time. This review has considered changes in both the *structural* and *functional* connectome in the context of AD-associated neurodegeneration as the primary example at three distinct stages, i.e., manifest disease, MCI prodrome, and the preclinical at-risk stage. At the disease stage, brain connectomic techniques have afforded a way to model the structural and functional failing integrity of specific neural subsystems and offered new insights into how

degenerative processes may spread through interconnected *networks* via central regions. Specifically, AD patients have shown disruptions in SC in important hub regions, interhemispheric regions, and fiber crossing regions. These changes are characterized by a reduced network *nodal degree*, change in white matter *path lengths*, and a decreased *global efficiency* of networks. During the MCI stages, evidence of the impact of intermediate neurodegeneration has been shown with regard to several network features including abnormal loss of white matter and significant changes in functional *network* organization. At the earliest stage, there is significant evidence of emerging changes reflected by differences between at-risk populations and cognitively healthy age-matched controls. These changes have been found primarily amid the interconnectivity between major RSNs, as well as differences in whole brain organization and *network* structure suggesting that connectomics level analysis is sensitive to subtle changes in brain *networks* before the onset of clinical symptoms. However, research on brain connectomics in disorders of cognitive aging remains at an early stage of development and new findings on changes in network features in preclinical and prodromal neurodegenerative diseases including non-AD and mixed types of disease will undoubtedly augment our knowledge in important ways relevant for clinical translation.

The present review also examines more recent developments such as the relationship to genetic markers, other multimodal imaging methods, and the emergence of dynamic *FC* which has aided the field in characterizing patient-specific abnormalities. The convergence of this information is likely to be beneficial for design of targeted interventions especially in heterogeneous diseases like AD and dementias of mixed etiology. Selective regional pathology plays an important role in the manifestations of different neurodegenerative diseases; and characterizing the progression to and from these brain regions during the advancement of neurodegeneration is important. Connectomics analysis is likely to be useful for enhancement of clinical trial designs by incorporating information about regional brain networks at baseline and after interventions. Connectomics analyses will also likely contribute to clinical trials by providing a dynamic metric that can (a) help identify subtle changes early in the disease course and (b) provide more comprehensive metrics to assess the impact of targeted therapeutic strategies.

In this review, we have illustrated the emerging utility of brain connectomics in providing new quantitative network features that can be used to detect specific structural and functional disruptions within brain circuitry including identification of white matter tracts and their integrity, the strength of functional connections between regions, and network disruption in unique RSNs. The future of brain connectomics holds significant promise in several areas. First, connectome studies may permit identification of early pathological changes that can predict disease progression. Second, due to the non-invasive nature of RS-fMRI and diffusion MRI, it is possible to collect data more easily and at more time-points to address long-term cognitive and behavioral changes and relate them to changes in the structural and functional connectome. Third, such studies offer insight into the unique characterization of different diseases identifying neurodegenerative signatures based on network features. To elaborate on the idea of a unique signature or “fingerprint,” brain connectomics may be well-suited to reveal individual differences in brain *networks* and to

help adapt therapeutic approaches centered on a person's baseline topological features and assess how treatment changes network topology, whether positively or negatively in terms of adverse side effects. In this way, connectome analysis may constitute a new approach that can guide the brain repair and recovery of brain *networks* especially as disease modifying interventions are developed.

Connectome-wide analyses hold promise of an unbiased means of characterizing brain *network* disturbances during manifest disease and in early preclinical and prodromal stages before onset of significant observable cognitive differences. However, this promise is likely to be realized with further improvements in imaging technology, statistical methodology, and integration of large-scale multimodal and dynamic data sets. Improving image quality will permit more precision in tracking changes in brain *networks* with disease progression, as well as to help resolve the directionality of fiber tracts with regards to SC. For SC, this will involve developing more accurate fiber reconstruction and tissue segmentation methodologies and also defining measures of connectivity that have a clear biological interpretation.

Further development of appropriate statistical methods is needed to allow better handling of complex data models, and the integration of multiple multimodal data sets as existing methodology is limited. Lastly, learning to account for the distinctive nature of dynamic data will be essential for the mapping of BOLD fluctuations in psychological states to their corresponding neurobiological states.

The young field of brain connectomics has been successful in generating evidence for aberrant *network* properties in early stage neurodegenerative diseases, demonstrating the potential for improved prediction of cognitive impairment, prior to onset of significant clinical symptoms. However, more clinical research is needed to refine methodology and validate the initial observations from patients with various neurodegenerative diseases at all stages. Eventually, follow-up studies linking in-vivo connectomics changes to post-mortem analyses of specific proteinopathies underlying many dementing disorders will be important. MRI sequences and post-processing methods will continue to evolve bringing significant improvement in accuracy and reliability, capacity for mapping more subtle changes in connectivity. All of these developments will facilitate the translation of intriguing research findings on connectome changes in cognitive aging and early stage disease to a level of development where they can contribute along with clinical assessment and other -omics and biomarkers to diagnosis and treatment monitoring as part of an evolving precision medicine.

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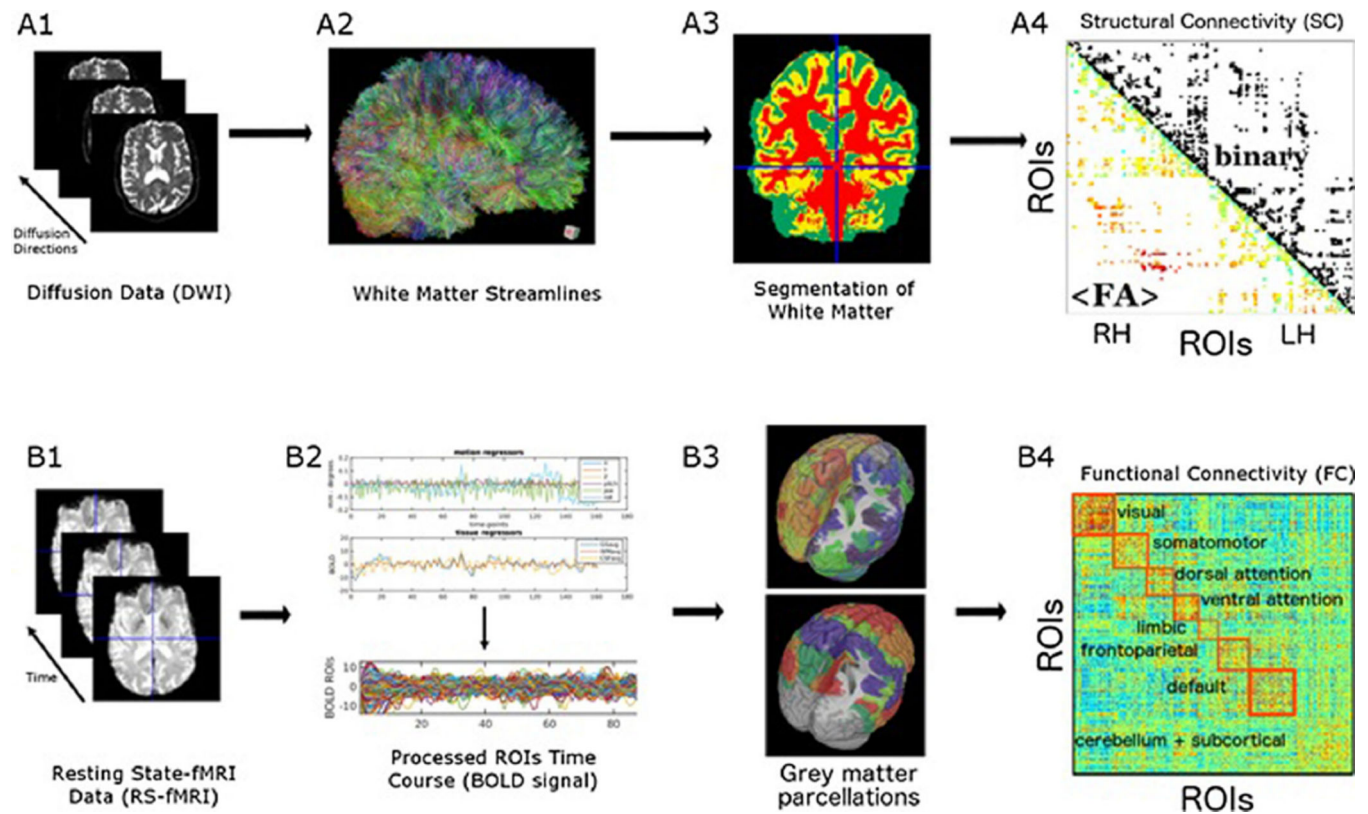


Fig. 1.

(A) *Top panel* denotes basic steps for processing of diffusion data. (A1) Different directions are taken in the scanner and combined; (A2) “streamlines” are obtained from this data and visualized using tractography (the more directions that can be obtained, the more accurate the data); (A3) using segmentation masks “streamlines” that fall within white matter are isolated; (A4) structural connectivity matrices can be obtained from the data in both binary and weighted form. The binary form is represented in the *upper triangular* where a dark dot denotes the presence of fibers connecting pairs of regions. The weighted form is represented in the *lower triangular* and denotes average fractional anisotropy (FA) values. (B) *Lower panel* denotes basic processing steps for RS-fMRI data. (B1) shows extracted time course from fMRI images; (B2) *top* shows BOLD signal isolated by regressing out nuisance variables, *shown on the bottom*; (B3) *top* shows an example of a gray matter parcellation, whereas *bottom* shows seven most prominent resting-state networks as reported by Yeo et al.; (B4) example of a resting-state functional connectivity matrix with rows and columns ordered according to those resting-state networks. *Red squares* highlight each of the RSNs

Table 1

Glossary for network terms in alphabetical order: network indices

Index	SC or FC measure	Definition
Cluster	SC and FC	Refers to a group of nodes that have denser connections with each other than with the rest of the network
Edge	SC and FC	Refers to a connection between nodes. Can either be weighted or binary
Fractional anisotropy (FA)	SC	A scalar value between 0 (indicating unrestricted diffusivity) and 1 that describes the degree of anisotropy of a diffusion process
Functional connectome	FC	A comprehensive map of correlated brain regions as measured by BOLD signals acquired using RS-fMRI studied as a network by means of a network science and graph theory
Global efficiency	SC	Related to the idea of the average shortest path is that of global efficiency, which is the inverse of the average shortest path. It is the overall information transfer efficiency across the whole network
Hub	SC and FC	A highly connected node. These nodes are relevant for efficient network communication, and damage to these nodes might be especially disruptive for network integrity
Independent component analysis (ICA)	FC	A statistical method that aims at decomposing multivariate signal into subcomponents. It has become useful in identifying resting-state networks by separating a signal into unique spatial and time components
K-core	SC and FC	A measure that assesses the overall connectedness of a network by identifying the most highly interconnected sub-networks within a global network
Modularity	FC	Modularity is revealed by subdividing the network into densely connected groups of nodes
Network	SC and FC	Graph comprising a set of nodes joined by a set of connections referred to as edges
Network core	SC and FC	Much like a cluster, a network core is a set of nodes that are highly and mutually interconnected
Node	SC and FC	The point at which two (or more) edges meet
Nodal degree	SC and FC	The amount of points at which two (or more) edges meet
Path/fiber length	SC	Describes the (shortest) path length between two nodes
Radial diffusivity	SC and FC	Derived from eigenvalues from the diffusion tensor and attempts to better capture white matter pathology by being sensitive to change in myelin in white matter
Rich club	SC	A collection of highly connected hubs, thought to be important for integration of information
Streamline	SC	A representation of a direct connection obtained through tractography (usually referring to white matter tracts)
Structural connectome	SC	A comprehensive map of anatomical white matter connections in the brain studied as a network by means of network science and graph theory

Table 2

Summary of connectivity studies included in review

Studies	Diagnosis	Modality	Network	Main findings	Significance
Sporns et al., 2005	Healthy controls	DWI	Structural	Research proposal that introduces the idea of displaying connections between brain regions as matrix	Introduces the term “human connectome” and the research strategy to achieve it
Biswal et al., 1995	Healthy controls	RS-fMRI	Functional	Confirm the existence of synchronous spontaneous fluctuations between primary and higher order somatosensory areas in the brain	First to identify resting-state networks
Beitzel et al., 2014	Healthy aging adults	DWI/RS-fMRI	Structural/functional	SC and FC evolve/re-organize with healthy aging	Indicates the close relationship between SC and FC and adds evidence to how age-related connectivity changes
Rose et al. 2000 Bozzali et al., 2002 Kiuchi et al., 2009 Ukmar et al., 2008	MCI and AD	DWI	Structural	Disruption of the white matter in important hub regions: cingulum bundle tract, corpus callosum, and the superior longitudinal fasciculus	Indicates a re-organization of important “hub” regions as a result of disease state
Douaud et al., 2011	MCI and mild AD	DTI	Structural	MCI show higher FA values in hub region, centrum semiovale region than controls	Diffusion MRI has the ability to detect sensitive changes in SC between disease states
Wang et al., 2015	MCI and AD	DTI/RS-fMRI	Structural/functional	Found disease stage specific changes in FC and SC. Further analysis showed FC changes (>coupling in anterior, <posterior brain regions) were positively correlated with SC changes (< FA, >MD) demonstrating an association between the two	Demonstrate specific patterns of interhemispheric changes between MCI and AD and the relationship between FC and SC
Liu et al., 2014	AD	RS-fMRI	Functional	Patients with severe AD were found to have reduced amplitude fMRI oscillations and reduced strength of FC, specifically in long-distance FC compared to mild AD patients (disease not as progressed)	Progression of disease can be modeled through looking at connectomics
Daianu et al., 2013	MCI and AD	DTI	Structural	Network nodal degree, normalized characteristic path length, and efficiency decreased with AD, while normalized small-worldness increased	Connectivity metrics can help understand whole brain network breakdown as cognitive impairment increases
Daianu et al., 2015	MCI and AD	DTI	Structural	AD patients were found to have an undisturbed structural core network	Demonstrates possible preservation and plasticity in diseased brains
Dzezgza et al., 2015	MCI	MRU/PET	Functional	Significant disruptions of whole brain connectivity were found in amyloid-positive patients with and without MCI in typical cortical hubs	Indicate that connectomics can capture early functional consequences of emerging molecular AD pathology before clinical symptoms
Brown et al., 2011	APOE ε4 carriers (at risk)	DTI	Structural	APOE ε4 carriers demonstrated an accelerated age-related loss of mean local interconnectivity compared to non-carriers as well as age-related loss in mean cortical thickness	Highlights a genotype-specific brain network pattern that can potentially affect the rate and/or spatial distribution of AD-related pathology
Wang et al., 2015	AD APOE ε4 carriers and AD APOE ε4 non-carriers	RS-fMRI	Functional	Whole brain graph analyses revealed that APOE ε4 significantly disrupted whole brain topological organization	Highlights how connectomics can help uncover genotype-specific abnormal functional brain network pattern in a preclinical population

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Studies	Diagnosis	Modality	Network	Main findings	Significance
Chen et al., 2015	HC (at risk)	DTI/RS-fMRI	Structural/functional	Reduced global efficiency was found in WM and marginally in FC (FC dysfunctions mainly in medial temporal areas) in <i>APOE</i> $\epsilon 4$ carriers	Connectomics helped demonstrate $\epsilon 4$ -specific abnormal structural and functional patterns despite no clinical diagnosis, which may potentially serve as biomarkers for early detection before the onset of the disease